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The simple 10-item PARC tool to predict childhood asthma – an external validation

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Abstract

Background

External validation of prediction models is important to assess generalisability to other populations than the one used for model development. The Predicting Asthma Risk in Children (PARC) tool, developed in the Leicestershire Respiratory Cohort (LRC), uses information on preschool respiratory symptoms to predict asthma at school age.

Objective

We performed an external validation of PARC using the Avon Longitudinal Study of Parents and Children (ALSPAC).

Methods

We defined inclusion criteria, prediction score items at baseline and asthma at follow-up in ALSPAC to match those used in LRC using information from parent-reported questionnaires. We assessed performance of PARC by calculating sensitivity, specificity, predictive values, likelihood ratios, area under the curve (AUC), Brier score and Nagelkerke's R-squared. Sensitivity analyses varied inclusion criteria, scoring items and outcomes.

Results

The validation population included 2690 children with preschool respiratory symptoms of which 373 (14%) had asthma at school age. Discriminative performance of PARC was similar in ALSPAC (AUC=0.77, Brier score 0.13) as in LRC (0.78, 0.22). The score cut-off of 4 showed the highest sum of sensitivity (69%) and specificity (76%) and positive and negative likelihood ratios of 2.87 and 0.41, respectively.

Changes to inclusion criteria, scoring items or outcome definitions barely altered the prediction performance.

Conclusion

Performing equally well in the validation cohort as in the development cohort, PARC is a valid tool for predicting asthma in population based cohorts. Its use in clinical practice is ready to be tested.

1. What is already known about this topic?

Several childhood asthma prediction models have been developed, but few have been externally validated.

2. What does this article add to our knowledge?

We found that the simple 10-item PARC asthma prediction tool performed equally well in a different study population and identified symptomatic preschool children who were likely to have asthma at school-age.

3. How does this study impact current management guidelines?

PARC is a simple non-invasive tool for predicting school-age asthma in symptomatic preschool children. It can be used to recruit high-risk children for clinical trials and its use in clinical practice is ready to be tested.

Keywords:

Asthma; Wheeze; Prediction; External Validation; PARC; Leicestershire Respiratory Cohorts; ALSPAC

List of abbreviations

PARC – Predicting Asthma Risk in Children

ALSPAC – Avon Longitudinal Study of Parents And Children

LRC – Leicestershire Respiratory Cohort study

ROC – Receiver Operator Curves

AUC – Area Under the Curve

PIAMA – Prevalence and Incidence of Asthma and Mite Allergy

MAS-90 - Multicentre Allergy Study

Introduction

Up to 40% of all preschool children have recurrent respiratory symptoms such as wheeze or cough but only about a quarter of these will have asthma at school age (1-4). Prediction models can be useful to identify those whose problems will persist. The ability to make an accurate prognosis can guide clinical decision-making and facilitate the selection of children for high-risk cohorts or clinical trials (5). Prediction models must be carefully developed using sound methodology for selecting prediction variables and examine discriminative performance and assess calibration (6). Prediction models may however not perform as well when applied to populations other than the ones they were developed in. External validation (in another population) is therefore necessary to assess the generalisability (7, 8).

Several models to predict later asthma in preschool children have been developed (9). Most use a combination of demographic information, symptoms and results of clinical tests (e.g. lung function or allergic sensitisation) (10-17). These models are useful for specialised clinical settings, where spirometry, body plethysmography and skin prick test can be done. Two tools use only demographic information and symptoms; information easily obtained from parental questionnaires or when taking patient history in a medical consultation, which makes these models more widely applicable (18, 19). One of these was developed by our group, the Predicting Asthma Risk in Children (PARC) tool. It was developed using data from the Leicestershire Respiratory Cohorts, a population-based cohort study from the United Kingdom (19). Four childhood asthma prediction models have been externally validated. The Asthma Predictive Index (API) (10) was validated in five external cohorts (11, 15, 20-

22), the PIAMA risk score (18) was validated in two external cohorts (21, 23), the Isle of Wight was validated in one external cohort (24) and the PARC tool was validated in a German asthma cohort, where it showed good predictive properties (25). However, this was a cohort, in which mothers with a history of allergy were overrepresented.

We aimed to validate PARC in a larger population based cohort in the Avon Longitudinal Study of Parents and Children (ALSPAC). We calculated measures of prediction performance and assessed the robustness of prediction performance to changes in the inclusion criteria, the prediction score items and the outcome.

Methods

We used the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines to report this external validation study (26).

Predicting Asthma Risk in Children (PARC)

The PARC tool was developed as a simple, low-cost, and non-invasive method to predict the risk of later asthma in symptomatic preschool children (19). It uses parental information about respiratory symptoms in 1-3 year old children to predict parental reported asthma five years later. The 10 scoring factors are: sex, age, wheeze without colds, number of wheezing episodes, shortness of breath due to wheeze, wheeze interfering with daily activities, exercise or allergy as triggers of wheeze, a history of eczema, and parental history of asthma and bronchitis. The published model was developed using the least absolute shrinkage and selection operator (LASSO) penalised logistic regression to avoid overfitting and simplified into

144 an easy-to-use tool. We validated the tool internally by using the leave-one-out
145 cross-validation method (19). The sample size was judged to be sufficient based on
146 the one-variable-per-ten-events rule, which suggests that at least ten outcome
147 events per potential predictor considered are needed, to develop a model that can
148 generalize to other samples (8). We considered 38 potential binary predictors (from
149 24 original variables) and the sample included 345 children with asthma.

150 **Development cohort, LCR**

151 As described previously (19), the PARC tool was developed using data from the
152 Leicestershire Respiratory Cohort study (LRC). The LRC is a longitudinal population-
153 based study from Leicestershire, United Kingdom (27). For the development of PARC,
154 we used data from 6808 children born in 1993-1997. Data for inclusion criteria,
155 prediction score items and outcomes came from questionnaires on respiratory
156 symptoms and general health that parents completed at baseline in 1998 and 1999
157 when the children were aged 1-3 and at follow-up in 2003 when the children were
158 aged 6-8 years. The Leicestershire Health Authority Research Ethics Committee
159 approved the study.

160 **External validation cohort, ALSPAC**

161 In the present study, we used data from the ALSPAC cohort to validate the PARC
162 tool. ALSPAC is a longitudinal birth cohort that recruited 14541 pregnant women
163 from Avon, United Kingdom, with expected delivery between April 1991 and
164 December 1992, resulting in 14062 live born children. The study has been described
165 in detail previously (28). Mothers and their partners filled in questionnaires about
166 their own and their child's health approximately yearly from when the children were
167 6 months old. We used baseline information from the questionnaires filled in when

the child was 1.5, 2.5 and 3.5 years to define inclusion criteria and calculate the prediction score and information from questionnaires completed at age 6 and 7 years to assess asthma at school age. The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees.

Inclusion criteria

We defined inclusion criteria for ALSPAC that resembled the inclusion criteria used in the LRC (**table 1)**. We included children aged 1.5 to 3.5 years from ALSPAC who had had wheeze or cough during the past 12 months (*Has your child experienced wheeze/cough during the past 12 months?*) and saw a doctor for one of these problems (answer category: *yes and saw a doctor*) plus had valid information on current wheeze and use of asthma medication at age 7.5 years.

Calculation of prediction scores

Items used for the prediction score are presented in **Table 3** for LRC and ALSPAC. In ALSPAC, the same questionnaires were sent to the parents at 1.5, 2.5 and 3.5 years of age. In order to achieve a comparable age distribution in ALSPAC as in the LRC, the baseline information was taken from the questionnaire filled at age 1.5 year for 28% of the study population, at age 2.5 for 57% and at age 3.5 for 15%. The age at which baseline information was taken for a given child, was obtained by random sampling ensuring this overall age distribution. Information on parental history of wheeze, asthma and bronchitis came from a questionnaire sent to the mother at 12 weeks gestation and from a questionnaire sent to the partner when the child was 33 months old. The prediction score was calculated as the sum of score-points from each item (**table 3**). We also assigned predicted probabilities for later asthma to these scores as suggested in our report on the development of PARC (19).

Definition of outcome

In the original cohort, we had defined the outcome 'asthma' as 'current wheeze plus use of asthma inhalers in the past 12 months'. To match this outcome definition in ALSPAC, we defined 'asthma' as 'yes' to the parent reported current wheeze ('*Has he/she had wheeze in the past 12 months'*) plus current use of asthma medication ('*Please indicate which of the following have been given to your child in the last 12 months? Asthma medication'*).

Assessing predictive performance

We assessed how well the calculated PARC prediction scores predicted later asthma in children from the ASLPAC cohort using measures of discrimination (the ability of the score to discriminate between children who had asthma at school age and those who had not) and calibration (the ability of the tool to predict the probability of later asthma) (8). To assess discrimination, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios for each possible cut-off value of the score. We also plotted receiver operator curves (ROC) and calculated area under the curve (AUC). To assess calibration, we assigned the probabilities of later asthma to each score value as proposed in the original article by Pescatore et al. (19). Based on these predicted probabilities, we first calculated maximum rescaled Brier score and Nagelkerke's R^2 as overall performance measures (8). These measures can be interpreted as "goodness-of-fit measures" showing how well the predicted probability approximates the outcome on a scale between 0 and 1, with 1 indicating perfect prediction and 0 representing a non-informative model, in which a constant probability equalling the prevalence of

the outcome is predicted for each child. Details on how to compute these measures are provided in the supplementary text E1. We examined calibration of the PARC tool graphically by plotting the predicted probability for each value of the score against the observed frequency of asthma among ALSPAC children with that score value, using the function calibrate.plot and val.prob.ci.2 from the 'gbm' package in R (29). We excluded children if they had missing information in any of the scoring variables (8%) apart from the item 'partner's history of wheeze, asthma and bronchitis', for which 25% had missing information. For these children, we set missing information about the partner to 'no history'.

In a separate analysis, we recalibrated the PARC scores in the ALSPAC cohort, by fitting a logistic regression of the outcome on the calculated scores (as a linear term) used in the main analysis above. For each child, we then calculated recalibrated scores as the value of the linear predictor from this regression. We then compared calibration performance of these scores with that of the original scores.

We used STATA 14 for data preparation and descriptive analysis and R version 2.1 to study model performance and model fit.

Sensitivity analyses

To test the robustness of PARC, we performed sensitivity analyses in ALSPAC and LRC datasets using alternative definitions of the included population, prediction score items and outcome definitions **(supplementary table E2)**. Firstly, we restricted age at baseline by including children aged 1.5 only, 2.5 only and 3.5 years only (only ALSPAC). Secondly, we altered the inclusion criteria to 1) any wheeze in the past 12 months, and 2) any cough in the past 12 months (only in ALSPAC). Thirdly, we

changed items in the prediction score by: 1) excluding 'wheeze triggered by exercise or allergy', as triggers of wheeze were measured differently in ALSPAC (open question) compared with LRC (specific response categories), and 2) exchanging 'wheeze without colds' with 'current wheeze' (only in LRC), 3) setting missing information in the prediction score items to the lowest value instead of excluding children with missing values in the analysis. Fourthly, we used an alternative outcome definitions: severe asthma (ALSPAC: current wheeze and use of asthma medication on at least 3 episodes, LRC: wheeze on at least 4 episodes and use of asthma inhalers).

Sample size

There are no guidelines for the adequate sample size needed for external validations of prediction model but according to a simulation study by Collins et al. (30) ideally 200 events are required. We had more than 300 events (asthma at age 7.5 years) in any of our analyses.

Results

Of the 14,541 children originally recruited in ALSPAC, 7200 children responded to the questionnaires at 1, 2, 3 and 7 years. Of these, 2921 fulfilled the inclusion criteria (saw a doctor for wheeze or cough in the past 12 months) and 2690 were included in our main analysis (231 were excluded due to missing information in one or more prediction score items). Not all questions used to specify inclusion criteria in the LRC were available in ALSPAC resulting in less restrictive inclusion criteria (**table 1**). **Table 2** shows similarities and differences between the two studies including location in the UK and the gender and age distribution. The two cohorts differed considerably in

ethnicity composition (98% whites in ALSPAC, 81% whites and 19% south Asians in LRC).

Distribution of PARC score

For most items of PARC we were able to use similar questions in ALSPAC as in the LRC (**table 3)**. There were some differences for 'wheeze without colds', questions on triggers for wheeze and parental history of wheeze and bronchitis. Assigning scores to ALSPAC children resulted in a more left skewed distribution of the PARC score in ALSPAC compared with the LRC (**Figure 1**). The maximum and median values were lower in the ALSPAC cohort (max = 13, median = 2, Interquartile range: 2-4) compared with the LRC cohort (max = 14, median = 4, Interquartile range: 2-6).

Frequency of asthma at follow-up

In ALSPAC, 373 (14%) of the included children had the primary outcome at age 7.5 years compared with 345 (28%) in LRC (**table 2**).

Performance of PARC main analysis

The discriminative ability of PARC was similar in ALSPAC and LRC (**figure 2**). ROC curves from ALSPAC and LRC were almost identical, AUC of 0.77 in ALSPAC and 0.78 in LRC. In ALSPAC, the score cut-off maximizing the sum of sensitivity (69%) and specificity (76%) was 4, in LRC the best cut-off was 5 (sensitivity 72%, specificity 71%). The validation analysis showed positive and negative predictive value of 0.32 and 0.94 and positive and negative likelihood ratios of 2.87 and 0.41, all at score cut-off 4 (discriminative values for all cut-off points in figure 2). Overall performance in

ALSPAC was comparable to that in LRC. The max-scaled Brier score was 0.13 in ALSPAC and 0.22 in LRC, the Nagelkerke's R-squared was 0.23 in ALSPAC and 0.28 in LRC. The calibration assessment showed that PARC scores from the ALSPAC population were associated with a lower frequency of later asthma than predicted from the LRC (**figure 3 and figure 4**). After recalibrating the predicted probabilities in ALSPAC (**figure 4B)**, our calibration plot showed good calibration of PARC in ALSPAC (Brier score = 0.17 for recalibrated main model).

Sensitivity analyses

Changes in inclusion criteria, prediction score items and definition of outcome resulted only in minor changes for most performance measures (**table 4**). In sensitivity analyses, PARC performed better in children aged 3.5 years (AUC = 0.78, $R^2 = 0.26$), compared with 1.5 year-olds (AUC = 0.71, $R^2 = 0.13$). Prediction was slightly worse in a population including only children who wheezed (AUC=0.73, $R^2 = 0.18$) compared with those who also saw a doctor or only children who coughed with or without seeing a doctor (AUC = 0.76, $R^2 = 0.20$). The exclusion of trigger variables in ALSPAC barely altered the performance. PARC performed better when the main outcome was severe asthma (AUC = 0.78, $R^2 = 0.23$). Sensitivity analysis where results excluding missing information were compared to results where missing information was set to zero showed no difference in the performance of PARC (data not shown).

Discussion

We found that PARC predicted asthma at school age equally well in the validation cohort, ALSPAC (AUC 0.77), compared with the development cohort, LRC (AUC 0.78). Using a cut-off score value of 4, PARC predicted asthma with a sensitivity of 69% and specificity of 76%, which was similar to what was found in LRC for a cut-off score of 5 (sensitivity = 72% and specificity = 71%). The calibration assessment showed that the observed frequency of asthma was generally lower in ALSPAC than predicted by the PARC score, but when we recalibrated the predicted probabilities to the ALSPAC population, agreement between predicted and observed asthma frequency was good.

Limitations and strengths

The information used to define the included population was not the same in ALSPAC as in LRC. Specifically, the ALSPAC cohort had insufficient information on night cough and cough without colds, so we replaced this information with a general question about cough. These relaxed inclusion criteria has led to inclusion of less severely affected children than the LRC population, which in turn explains the lower prevalence of asthma at school age (14% in ALSPAC compared with 28% in LRC). This did not affect the discriminative ability of PARC, but it affected calibration and the overall performance measures such as the Brier score. Furthermore, we lacked perfectly matched information on items needed to compute the PARC score. Key information for the score such as wheeze without colds and triggers of wheeze were not available in the same detail. However, our sensitivity analysis in ALSPAC suggested that exclusion of triggers of wheeze did not affect the performance much (AUC 0.77, same as main analysis).

A strength of our study was that we had full access to all data from the development and the validation cohort, which made it possible to compare the populations and assess discriminative performance and calibration of PARC directly. Secondly, the cohort used for the external validation was large and had collected questionnaire information yearly between birth and the age of 8 years. This enabled us to match and vary the age at which baseline and outcome information were collected. Thirdly, less than 5% of the information in the single variables used for scoring (apart from partner's history of asthma and wheeze) was missing and we therefore excluded only a small number of the children satisfying the inclusion criteria (8%). Sensitivity analysis, in which missing information was set to zero, did not change our main results. Fourthly, for the primary outcome, we had perfectly maching on current wheeze and use of asthma medication at the age of 7.5 years, and we could therefore rule out that differences in performance of the PARC tool in ALSPAC and LRC cohorts were caused by different outcome definitions.

Comparison with other studies

One other study has investigated the external validity of PARC and found similar performance compared with the original cohort (25). The study used information from the German Multicentre Allergy Study (MAS-90) birth cohort with an overrepresentation of children from allergic parents. The authors included 140 children in their validation population. The authors found that PARC predicted asthma with AUC= 0.83 and a sensitivity of 0.82, a specificity of 0.69 at a score of 5.

The calibration assessment showed good agreement between predicted probabilities of asthma and observed frequency.

Of the other models developed to predict asthma in children, three have been externally validated (supplementary table E3). The Asthma Predictive Index developed using the Tucson Children's Respiratory Study in 2000 (10) was externally validated in five separate studies (11, 15, 20-22), showing generally higher sensitivity, but lower specificity than in the development cohort, which could partly be explained by differences in inclusion criteria. Caudri et al. developed an asthma prediction model using the Prevalence and Incidence of Asthma and Mite Allergy birth cohort (PIAMA) (18), which was externally validated in a Columbian clinical cohort of children with wheeze (21) and in the Dutch population-based Generation R study (23) and showed similar performance compared with the development cohort. The calibration assessment showed that the PIAMA risk score systematically overestimated asthma risk at age 7 years. Kurukulaaratchy et al. developed a prediction model in the Isle of Wight birth cohort (13), which was applied in the British Multicentre Allergy Study (MAS) birth cohort, where calibration showed different predictive properties compared with the development cohort. The evidence from these external validation studies and the present study suggests that these prediction models are generally robust in different populations and discriminate asthma from no asthma well in different settings, but calibration must be assessed for the models to accurately predict asthma risk. Among the existing prediction models that have been externally validated, PARC and the PIAMA risk score are the models most easily applied in practice as they require no specific physiological measurements or blood investigations as does for example the API

(supplementary table E3). Additionally, PARC predicts as well or better than other existing asthma prediction tools when comparing the combined sensitivity and specificity using the Youden Index (31) (sensitivity + specificity – 1, calculated based on the maximal sum of sensitivity and specificity), which ranges from 0 to 1 with 1 indicating perfect prediction. Reported values of the Youden index are 0.43 for PARC compared with 0.32 for the API, 0.36 for the PIAMA risk score and 0.38 for the Isle of Wight score (19). PARC has a similar positive likelihood ratio (true positives/false positives) (+LR = 2.5) compared with the PIAMA risk score (+LR = 2.5) but lower than the API (+LR = 7.8) and the Isle of Wight (+LR = 3.4) (supplementary table E3). These differences could be due to different inclusion criteria used for the study populations in which the prediction scores were developed. The API was developed in a general population sample including mostly healty children. Such a population has a a low baseline risk of asthma at follow-up whereas the populations used for PARC and the PIAMA score included only children visiting doctors for wheeze or chronic cough who thus had a higher baseline risk of asthma at follow-up. In a population with low baseline risk, it may be easier to correctly identify those that will not develop asthma, which increases specificity and, assuming the same sensitivity, increases the positive likelihood ratio. Also, the positive likelihood ratio can be interpreted as the ratio of posterior odds (after a model predicts that a child will have asthma based on baseline information) of having later asthma to the prior odds (ignoring baseline information). A higher positive likelihood ratio is needed to achieve the same posterior likelihood of asthma if the baseline risk is low compared to when it is high.

406

407 **Interpretation**

408 PARC predicted asthma better in children who were older at the baseline survey. A
409 reason for this could be that the aetiology of wheeze in children age less than 2
410 years is more heterogeneous and only a small proportion will eventually have
411 asthma. In a study using data from ALSPAC, Henderson et al. (32) investigated
412 wheezing phenotypes over time and found a majority of children with the
413 phenotype *transient early wheeze* begin wheezing in the first two years of life. In our
414 data we saw that more children fulfilled our inclusion criteria early in life (3583 1.5-
415 year-olds compared to 2238 3.5-year-olds), but the proportion of children that had
416 asthma at school age was lower among children aged 1.5 years initially (12%) than in
417 children aged 3.5 years at baseline (19%). This may explain the poorer prediction,
418 particularly poorer calibration, among 1.5 year-olds.
419 The different phenotypes of wheeze might also explain why the predictive
420 performance of PARC was better for severe asthma. Several studies have identified a
421 phenotype characterised by persistence of symptoms from an early age (3, 32, 33).
422 Children with this phenotype tend to have more wheezing episodes, more often use
423 bronchodilators, and cough without colds compared with wheeze phenotypes with
424 late onset transient or viral wheeze. Because severity tends to track (34), PARC
425 identifies those with more severe disease at school age because these children often
426 had already severe symptoms early in life. As disease burden is greater in children
427 with severe asthma, they are the main target group for interventions.
428 The discriminative ability of PARC appears robust to changes in item and population
429 definitions. Although different questions were used in the two cohorts, they

probably measure similar concepts. This makes PARC useful also in settings with misclassification of information. Outcome prevalence appears to be the more critical factors affecting predictive performance. Therefore, if PARC is to be used in a population with outcome-prevalence very different from that in LRC, we recommend simple recalibration of the PARC, which allows obtaining risk-probabilities that are closer to the observed frequencies. Practically, one approach for calibration could be to examine the prevalence of school-age asthma in the population in question and compare it to LRC or ALSPAC. If the observed frequencies are similar to those in LRC or ALSPAC, the predicted probabilities calculated in the original study or this validation study can be used. If the prevalence is much higher or much lower, it might be necessary to collect (possibly retrospectively from medical records) information from a subsample of children to fill in the PARC tool and thereby calculate new predicted probabilities.

The ALSPAC cohort did not offer the possibility to validate the PARC tool in different ethnic groups as the ALSPAC included 98% whites. The PARC tool would need to be externally validated in a sample with a larger ethnic diversity to determine the generalizability of PARC in different ethnic settings.

The sample size in the original development of the PARC prediction model was estimated to be sufficient according to the one-variable-per-ten-events rule with 24 potential predictor variables (represented by 38 binary variables) and 345 events (35). However, the appropriateness of this rule has been questioned (36). It is possible that our original study did not have sufficient statistical power to identify some important predictors among the 38 predictors considered, although 10 of these were retained in the final model and are used in the PARC tool. That the PARC

tool includes irrelevant predictors as a result of overfitting is less likely as we used penalised logistic regression to build the tool. Furthermore, almost all predictors included in PARC are either recognised risk factors (male sex, parental history) or are indicators of atopy or symptom severity, which are both known to be associated with persistence. The only exception is older age (≥ 1 year), which is a plausible predictor, as wheeze or cough in infancy is more transient and usually associated with respiratory infections.

Conclusion

This validation study showed that PARC has the same ability to identify preschool children who are likely to develop asthma at 7.5 years in a population different from the development cohort. The discriminative ability of the tool appears to be robust to changes in inclusion criteria, scoring variables and outcome definitions suggesting that PARC is robust to misclassification of information. Our study suggests that the tool may need recalibration when applied to populations, in which the outcome prevalence differs greatly from the development cohort. PARC is a valid tool for predicting asthma in pre-school children and its use in clinical practice is ready to be tested.

Ethics approval and consent to participate

The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees. The Leicestershire Health Authority Research Ethics Committee approved the Leicestershire Respiratory Cohort study.

Authors' contributions

EP, BS, and CK made substantial contributions to the study conception and design and were involved in the drafting of the manuscript. AR contributed to the study management and data preparation. EP, BS and FH were responsible for the statistical analyses. JH and RG were involved in data collection and preparation of ALSPAC. EP, BS, FH, CJ, AR, EG, JH, RG and CK critically revised and approved the manuscript.

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496

497 **Availability of data and material**

498 The LRC dataset is available on reasonable request by contacting Claudia Kuehni. The
499 ALSPAC dataset is available by proposals through the ALSPAC Executive Committee
500 using the procedures outlined in the ALSPAC Access Policy
501 (www.bristol.ac.uk/alpsac/researchers/access/)

502

503 **Figure legends**

504 **Figure 1:** Distribution of the PARC scores* (relative frequency) in the external
505 validation population (ALSPAC, n=2690, black) and original development population
506 (LRC, n=1226, grey).

507

508 **Figure 2:** Receiver operating characteristic (ROC) from validation population ALSPAC
509 (solid line) and the original development population LRC (dashed line). Numbers (1-
510 13) indicate asthma prediction score values and their corresponding positions
511 (indicated in red on the figure). The area under the curve (AUC) corresponds to the
512 primary outcome in both cohorts. The table above the figure shows sensitivity
513 (Sens), specificity (Spec), positive and negative predictive values (PPV, NPV) and
514 likelihood ratios (LR+, LR-) for each score point in ALSPAC.

515

516 **Figure 3:** Predicted probability of developing asthma at follow-up in LRC (dashed
517 grey line) and probabilities predicted by the recalibrated model in ALSPAC (black
518 line).

519

520 **Figure 4**: Calibration assessment of predicted probabilities vs. observed asthma
521 frequencies in seven equally sized groups. Figure A displays the calibration
522 assessment for the predicted probabilities calculated in LRC. Figure B displays the
523 probabilities predicted by the recalibrated model in ALSPAC. Shaded areas represent
524 exact pointwise 95%-CI for asthma frequency. The diagonal red line represents
525 perfect calibration.

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Table 1: Inclusion criteria and outcome definitions in LRC and ALSPAC

LRC: items for inclusion criteria* (at age 1-3 years)	**Answer categories**	**ALSPAC: items for inclusion criteria* (at age 0.5, 1.5, 2.5 years)**	**Answer categories**	**Comparability**
Has your child had wheezing or whistling in the chest in the last 12 months?	Yes, no	Has he had any of the following the last 12 months, wheezing?	Yes and saw a doctor Yes but did not see doctor No did not have	Good
Does your child usually have a cough without colds?	Yes, no	Has he had any of the following the last 12 months, cough?	Yes and saw a doctor Yes but did not see doctor No did not have	Moderate
In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?	Yes, no	No question	-	-
How often did your child see a GP for coughing or wheezing during the last 12 months?	Never, once, 2-3 times, 4-6 times, 7 or more times	Has he had any of the following the last 12 months, wheezing?	Yes and saw a doctor Yes but did not see doctor No did not have	Good
In the last 12 months, has wheezing or asthma resulted in your child: (4 categories: referred/admitted to hospital, attending/calling ER or GP)	Yes, no	No question	-	-
LRC: items for outcome definition@ (at 8 years)	**Answer categories**	**ALSPAC: items for outcome definition@ (at 7.5 years)**	**Answer categories**	**Comparability**
Has your child had wheezing or whistling in the chest in the last 12 months?	Yes, no	Has he had any of the following in the past 12 months, wheezing?	Yes and saw a doctor Yes but did not see doctor No did not have	Very good
Did your child take any of the following during the last 12 months? (4 categories: inhalers by content/type)	Yes, no, don't know	Please indicate which of the following have been given to your child the last 12 months. - Asthma medication?	Never Yes for 1-2 episodes only Yes for 3 or more episodes	Very good

***Inclusion criteria LRC**: Wheeze or cough (cough without colds or cough at night) with 1 or more visits to the doctor for wheeze or cough during the past 12 months). **Inclusion criteria ALSPAC:** Wheeze or cough during the past 12 months and saw a doctor for one of these problems (answer category: yes and saw a doctor). **@Outcome definition LRC:** 'Yes' to wheeze and use of asthma medication past 12 months. Outcome definition ALSPAC: **Outcome definition ALSPAC**: 'Yes' to wheeze and use of asthma medication past 12 months.

Table 2: Comparison of study characteristics and demographic factors in development cohort (LRC) and external validation cohort (ALSPAC)

	Development cohort (LRC) N=1226	**Validation cohort (ALSPAC) N=2690**
Location	Leicestershire (United Kingdom)	Bristol (United Kingdom)
Study design	Prospective cohort (from birth)	Prospective cohort (from pregnancy)
Recruitment	General population random sample	General population random sample
Year of birth	1995-1997	1991-1992
Sex		
male	678 (55)	1433 (54)
Ethnicity		
White	797 (69)	2580 (98)
South Asian	305 (26)	-
Other	57 (5)	52 (2)
Baseline Assessment		
Age®		
1 year	336 (27)	763 (28)
2 years	702 (57)	1516 (56)
3 years	188 (15)	411 (15)
Wheeze* prevalence	766 (62)	791 (29)
Cough* prevalence	1085 (89)	2654 (99)
Follow-up Assessment		
Age		
6 years	336 (27)	
7 years	702 (57)	2690 (100)
8 years	188 (15)	
Wheeze* prevalence	427 (35)	451 (17)
Cough* prevalence		
Use of asthma medication*	345 (28)	586 (22)
Wheeze* + use of asthma medication*	345 (28)	373 (14)

This table is displayed using n (%) unless otherwise stated. ®The age distribution at baseline in ALSPAC was matched to the baseline age distribution in LRC, * in the past 12 months. Prevalence of wheeze and cough is so high, because only children with lower respiratory symptoms were included.

Table 3

Table 3: Questionnaire items used for scoring and their distribution in LRC and ALSPAC

Item Nr.	Question item in LRC	Score value	(%)	Questionnaire item in ALSPAC	Score value	(%)	Comparability
1	What is the child's sex	Female = 0	(45)	Sex	Female = 0	(47)	Perfect
		Male = 1	(55)		Male = 1	(53)	
2	How old is the child?	1 years = 0	(27)	Age	1 years = 0	(28)	Perfect
		2 years = 1	(57)		2 years = 1	(57)	
		3 years = 1	(15)		3 years = 1	(15)	
3	In the last 12 months, has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0 Yes = 1	(82) (18)	Since she was 6/18/30* months old has she had any periods when there was wheezing with whistling on her chest when she breathed?	No = 0 Yes = 1	(71) (29)	Moderate. Question does not include 'without cold'
4	How many attacks of wheeze has the child had during the last 12 months?	0-3 = 0 >3 = 2	(77) (23)	Has your baby ever had wheezing with whistling on her chest when she breathed? b) How many separate times has this happened	0-3 = 0 >3 = 2	(82) (18)	Very good
5	In the last 12 months, how much did wheezing interfere with your child's daily activities?	Never=0 A little = 1 A lot = 2	(64) (26) (10)	Proxy: 'how many days altogether would you say he had wheezed in the past 12 months?'	0-3 days = 0 4-19 days = 1 20 or more days = 2	(77) (16) (7)	Poor. Different question.
6	Do these wheezing attacks cause him/her to be short of breath?	Never = 0 Sometimes = 2 Always = 3	(65) (29) (6)	Since she was 6/18/30* months old has she had any periods when there was wheezing with whistling on her chest when she breathed? d) Was he breathless (struggling for breath) during any of these times?	No for all = 0 Yes for some = 2 Yes for all = 3	(84) (15) (1)	Very good
7	In the last 12 months, did exercise (playing, running) or laughing, crying or excitement cause wheezing or coughing in the child?	No = 0 Yes = 1	(61) (39)	has your baby ever had wheezing with whistling on her chest when she breathed? g) what do you think brings them on? (exercise, emotion)	No = 0 Yes = 1	(99) (1)	Moderate. Optional free text field – few answers
8	In the last 12 months, did contact with dust, grass, pets or other animals cause wheezing or coughing in the child?	No = 0 Yes = 1	(93) (7)	has your baby ever had wheezing with whistling on her chest when she breathed? g) what do you think brings them on? (allergy)	No = 0 Yes = 1	(99) (1)	Moderate. Optional free text field – few answers
9	Has the child ever had eczema?	No = 0 Yes = 1	(57) (43)	Has the baby had a rash in the joints and creases of her body (e.g. behind the knees, under the arms)?	No = 0 Yes = 1	(71) (29)	Good. Asking about rash instead of eczema
10	Has the child's parents ever suffered from wheezing, asthma or bronchitis?	None = 0 Mother = 1 Father = 1 Both = 1	(52) (17) (22) (9)	Have you ever had any of the following problems: asthma/ Wheezing past 2 years Have you had wheeze or bronchitis since the child was born (8 month after birth)	None = 0 Mother or father = 1 Both = 1	(65) (31) (4)	Moderate. Information asked from partner instead of father.

*ages correspond to age 12 months prior to questionnaire mailing

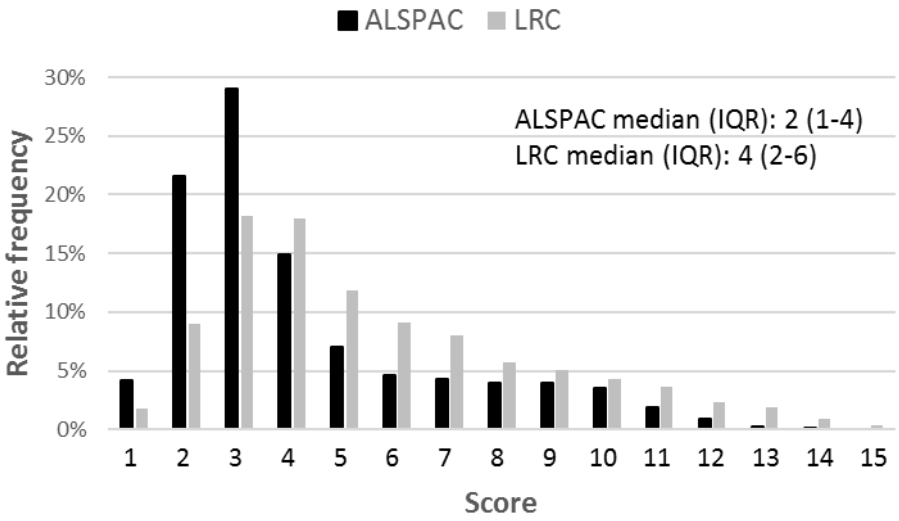
Table 4 - Unmarked

Table 4: Predictive performance of PARC for main analysis and sensitivity analyses in ALSPAC and LRC (definitions of main and sensitivity analyses in table E1)

	ALSPAC	n	Cases (%)	Sens	Spec	PPV	NPV	LR+	LR-	AUC	R^2	Brier score
A1	**Main analysis**	2690	373 (14)	0.69	0.76	0.32	0.94	2.87	0.41	0.77	0.23	0.13
A2	**Altered inclusion criteria**											
A2.1	Only children aged 1 year	3583	439 (12)	0.51	0.80	0.26	0.92	2.53	0.61	0.71	0.13	0.06
A2.2	Only children aged 2 years	2817	410 (14)	0.69	0.72	0.29	0.93	2.42	0.44	0.76	0.21	0.07
A2.3	Only children aged 3 years	2238	396 (19)	0.62	0.82	0.43	0.91	3.46	0.46	0.78	0.26	0.21
A2.4	Wheeze past 12 months	1423	326 (23)	0.81	0.46	0.31	0.89	1.49	0.42	0.73	0.18	0.08
A2.5	Cough past 12 months	6351	554 (9)	0.52	0.87	0.28	0.95	4.11	0.55	0.76	0.20	0.07
A3	**Altered scoring variables**											
A3.1	Exclude trigger variables	2690	373 (14)	0.69	0.76	0.32	0.94	2.89	0.41	0.77	0.23	0.13
A4	**Altered outcome definition**											
A4.1	Severity: Wheeze past 12 months and use of asthma medication at 3 or more episodes	2688	307 (11)	0.70	0.75	0.26	0.95	2.78	0.40	0.78	0.23	0.06
	LRC											
L1	**Main analysis**	1226	345 (28)	0.79	0.57	0.42	0.87	1.83	0.38	0.78	0.28	0.22
L2	**Altered inclusion criteria**											
L2.1	Wheeze past 12 months	1033	330 (32)	0.72	0.53	0.42	0.80	1.52	0.53	0.69	0.17	0.14
L3	**Altered scoring variables**											
L3.1	Exclude trigger variables	1226	345 (28)	0.74	0.63	0.44	0.86	2.04	0.40	0.77	0.28	0.22
L3.2	Exchange wheeze without colds with current wheeze	1226	345 (28)	0.82	0.53	0.40	0.88	1.73	0.34	0.77	0.28	0.21
L4	**Altered outcome definition**											
L4.1	Severity: Wheeze past 12 months more than 4 episodes and use of asthma medication	1030	86 (8)	0.86	0.61	0.17	0.98	2.19	0.23	0.84	0.32	-0.15*

Sens, Spec, PPC, NPV, LR+, LR- are all presented for PARC score = 4. Abbreviations; R^2: Nagelkerke's, Sens: sensitivity, Spec: Specificity, PPV: positive predictive value, NPC: negative predictive value, LR-: Negative likelihood ratio, LR+: positive likelihood ratio. *The negative scaled Brier score is due to the large difference in the prevalence of the outcome in main analysis and the corresponding sensitivity analysis.

Figure 1 - Unmarked



*Score based on items described in table 3 for ALSPAC and LRC, respectively. Abbreviations; ALSPAC: Avon Longitudinal Study of Parents and Children, LRC: Leicestershire Respiratory Cohorts, IQR: Interquartile range

Figure 2 - Unmarked

	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Sens	1.00	0.98	0.91	0.79	0.69	0.61	0.53	0.46	0.38	0.27	0.14	0.06	0.01	0.00
Spec	0.00	0.05	0.28	0.60	0.76	0.83	0.87	0.91	0.94	0.97	0.99	1.00	1.00	1.00
PPV	0.14	0.14	0.17	0.24	0.32	0.36	0.39	0.44	0.50	0.56	0.65	0.69	0.63	1.00
NPV	-	0.95	0.95	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.86
LR+	1.00	1.03	1.27	1.97	2.87	3.51	3.94	4.95	6.30	7.96	11.57	13.67	10.35	-
LR-	-	0.35	0.31	0.35	0.41	0.47	0.55	0.59	0.66	0.76	0.87	0.95	0.99	1.00

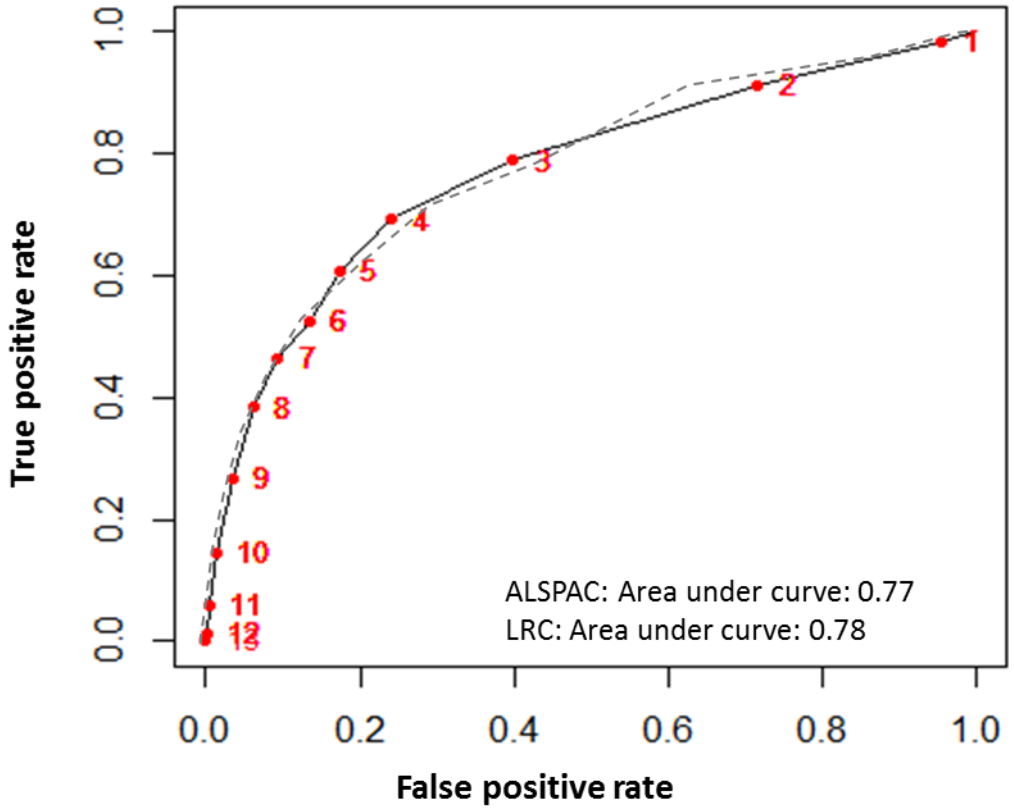


Figure 3 - Unmarked

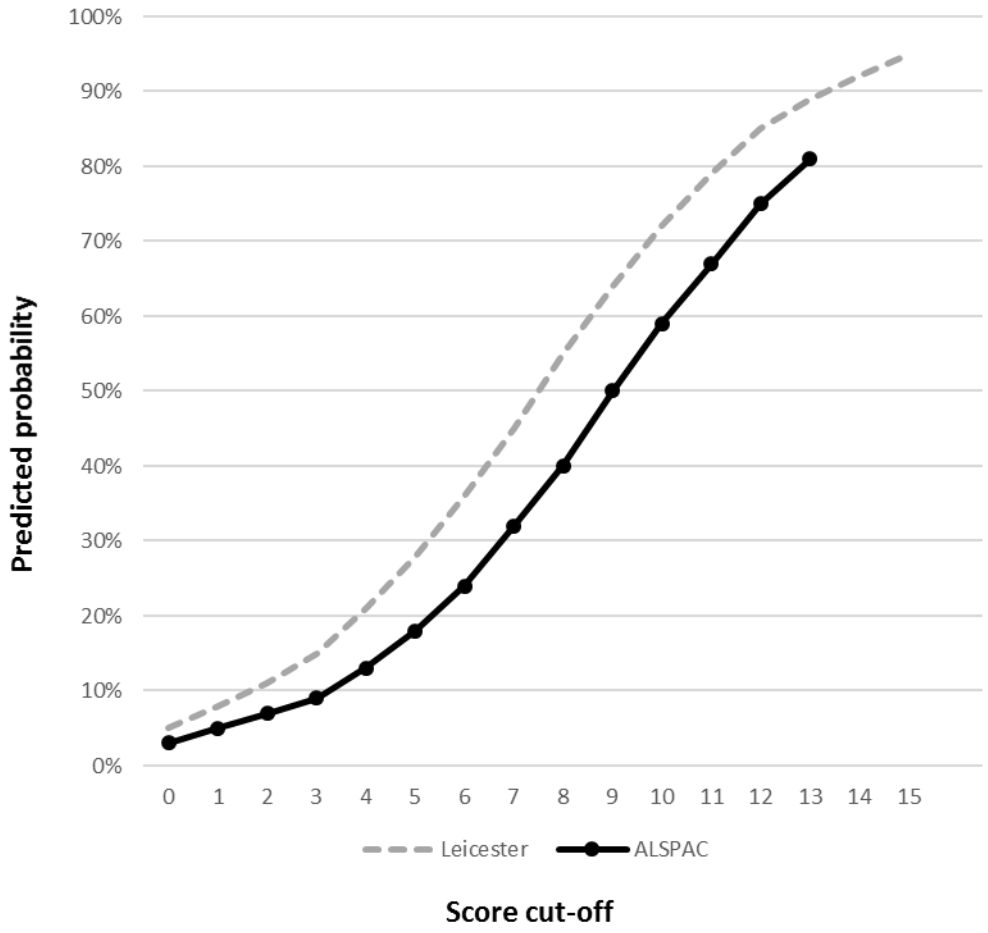
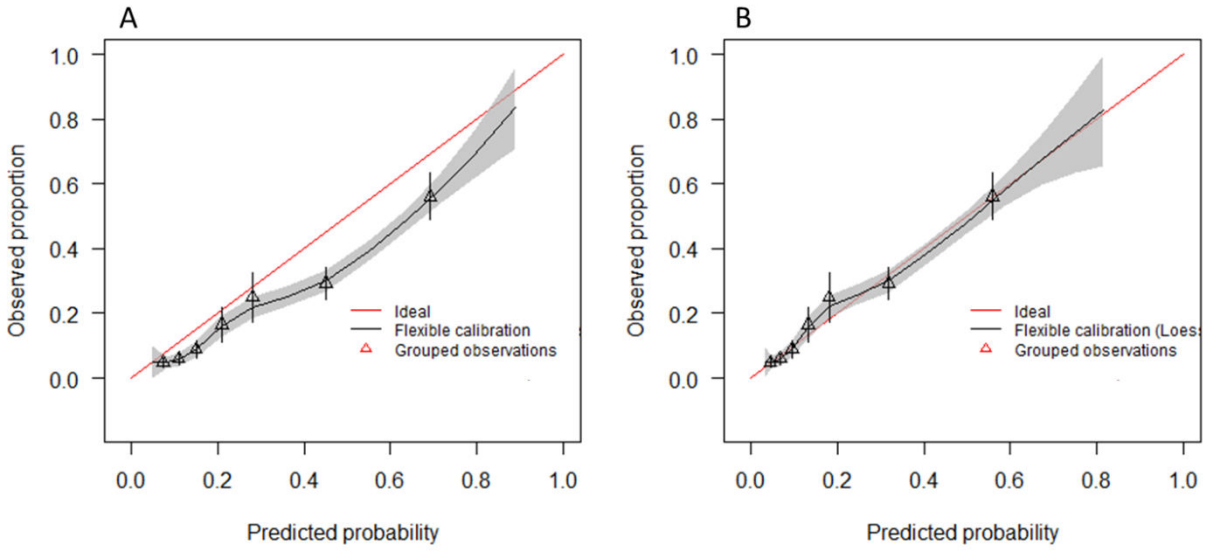


Figure 4 - Unmarked



Supplemental Text E3:

Definition of the scaled Brier score and Nagelkerke's R^2

In the following, let y_i represent the outcome for child i taking on the value 1 if the child has later asthma and 0 otherwise, and p_i the predicted probability based on the baseline information of that child using the PARC tool. Let n be the total number of children in the cohort and $\bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i$ be the prevalence of the outcome.

Scaled Brier score

The Brier score evaluates the mean squared error of prediction[1]:

$$Brier = \frac{1}{n}\sum_{i=1}^{n}(p_i - y_i)^2$$

This score takes on the minimum value of 0 when p_i predicts y_i perfectly. To obtain a similar interpretation for this statistic as for R^2 in linear regression models, we rescale this score as

$$Brier_{scaled} = 1 - \frac{Brier}{Brier_{max}}$$

where $Brier_{max}$ is the Brier score evaluated with $\bar{y}$ replacing p_i in the formula above. $Brier_{scaled}$ takes on values between 0 and 1 with 1 representing perfect prediction and 0 a non-informative prediction model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$.

Nagelkerke's R^2

Nagelkerke's R^2 compares the likelihood of the prediction model with that of a non-informative model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$. It is calculated as follows[1, 2]:

$$R^2_{NK} = \frac{1 - \left(L_0/L_1\right)^{2/n}}{1 - (L_0)^{2/n}}$$

Where L_1 and L_0 are the likelihood of PARC and the non-informative models respectively. The denominator of this equation is simply used for rescaling and represents the maximum value that the numerator can attain (in a perfect model $L_1 = 1$). As $Brier_{scaled}$, the statistic R^2_{NK} thus takes on values between 0 and 1 with 1 representing perfect prediction and 0 the non-informative model. The likelihood function evaluated for the predictions of the PARC tool is given by:

$$L_1 = \prod_{i-1}^{n} p_1^{y_i}\,(1 - p_i)^{(1-y_i)}$$

L_0 is calculated by replacing p_i with $\bar{y}$ in this formula.

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Table E2 (supplementary): Overview of the definitions of main analysis and sensitivity analyses in ALSPAC and LRC.

	Analysis	Definition changed	Definition
	ALSPAC		
A1	**Main Analysis**	-	**Inclusion criteria**: Wheeze or Cough in the past 12 months and saw a doctor for this. **Scoring variables:** 1)Sex 2)age 3)wheeze past 12 months 4)number of wheeze attacks 5)number of days wheezed 6)breathless due to wheeze 7)exercise as trigger for wheeze 8)allergy as trigger for wheeze 9)rash in the joints 10)family history of asthma or bronchitis. **Outcome definition**: Wheeze past 12 months and use of asthma medication.
A2	**Altered inclusion criteria**		
A2.1	Only children aged 1 year	Inclusion criteria	Age excluded as prediction variable
A2.2	Only children aged 2 years	Inclusion criteria	Age excluded as prediction variable
A2.3	Only children aged 3 years	Inclusion criteria	Age excluded as prediction variable
A2.4	Wheeze past 12 months	Inclusion criteria	Past 12 months: *Has he/she had periods when there was wheezing with whistling on his/her chest?* or *Has he/she had wheeze?*
A2.5	Cough past 12 months	Inclusion criteria	Past 12 months: *Has he/she ever had a time when he has coughed on and off for at least 2 days?* or *Has he/she had cough?*
A3	**Altered scoring variables**		
A3.1	Exclude trigger variables	Scoring variables	Exclude item 7 and 8: Exercise and allergy as triggers for wheeze
A4	**Altered outcome definition**		
A4.1	Severity: Wheeze past 12 months and use of asthma medication at 3 or more episodes	Outcome	*Has he had wheeze in the past 12 months?* AND *Please indicate which of the following have been given to your child in the past 12 months* (answer category: asthma medication, on 3 or more episodes)
	LRC		
L1	**Main analysis**	-	**Inclusion criteria:** Wheeze or cough apart from colds in the past 12 months and saw a doctor for wheeze or cough. **Scoring variables:** 1)Sex 2)age 3)wheeze apart from colds 4)number of wheeze attacks 5)wheeze interference with daily life 6)shortness of breath due to wheeze 7)exercise or emotion as trigger for wheeze 8)allergy as trigger for wheeze 9)child ever had eczema 10)family history of wheeze, asthma or bronchitis. **Outcome:** wheezing or whistling in the chest in the last 12 months AND use of asthma medication
L2	**Altered inclusion criteria**		
L2.1	Wheeze past 12 months	Inclusion criteria	*Has your child has wheezing or whistling in the chest in the last 12 months*?
L3	**Altered scoring variables**		
L3.1	Exclude trigger variables	Scoring variables	Exclude item 7 and 8: Exercise and allergy as triggers for wheeze
L3.2	Exchange wheeze without colds with current wheeze	Scoring variables	Exchange item 3 'wheeze without colds' with 'wheezing or whistling in the chest in the last 12 months'
L4	**Altered outcome**		
L4.1	Severity: Wheeze past 12 months more than 4 episodes and use of asthma medication	Outcome	More than 4 episodes of wheeze past 12 months and use of asthma medication past 12 months

Supplementary table E3: Comparison of four asthma prediction tools for preschool children

	PARC	**API***	**Isle of Wight**	**PIAMA**
No. (included in analysis)	1226	776	336	2054
Inclusion criteria				
Age (y)	1-3	2-3	4	1-4
Symptoms	Health care visit because of respiratory problems plus ≥1 of the following: wheeze, cough without colds, cough at night	Entire cohort (including a majority of children without symptoms)	Wheeze at ages 1,2 and 4 y	Wheeze or cough at night without colds in the past 12 months
Outcome definition				
Age (y)	6-8	8	10	7-8
Prediction interval (y)	5	5	6	3-7
Criteria	Wheeze plus asthma medication (past 12 months)	Doctor's diagnosis of asthma plus current wheeze or >3 episodes of wheeze (past 3 months)	Current wheeze	At ages 7 and 8 y: current wheeze or prescription of inhaled corticosteroids or doctor's diagnosis of asthma (past 12 months)
Outcome prevalence	28%	14%	37%	12%
Predictor variables included in tool	Male sex, age, wheeze without colds, frequent wheeze, activity disturbance, shortness of breath, exercise-related wheeze/cough, aeroallergen-related wheeze/cough, eczema, parental asthma or bronchitis	Wheeze, frequent wheeze, wheeze without colds, eczema, parental asthma, blood eosinophilia, allergic rhinitis	Family history of asthma, recurrent chest infections (at 2 y), skin prick test positive (at 4 y), nasal symptoms (at 1 y)	Male sex, post term delivery, wheeze/dyspnea without colds, frequent wheeze, eczema, respiratory infections, inhalation medication (parents), parental education
Method used to derive tool	Penalized logistic regression	Combination of predictors was chosen that yielded the highest PPV and specificity	Stepwise backward logistic regression	Stepwise backward logistic regression
Performance measures	Score cutoff ≥5	Loose API	Score cutoff ≥3	Score cutoff ≥20
Youden index	0.43	0.32	0.38	0.36
Sensitivity (%)	72	51	53	60
Specificity (%)	71	81	85	76
PPV (%)	49	29	68	23
NPV (%)	86	91	74	94
+LR	2.48	7.43	3.41	2.50
-LR	0.39	0.75	0.56	0.53

PARC: Predicting Asthma Risk in Children (19), API: Asthma Predictive Index (10), Isle of Wight risk score (13), PIAMA risk score (18), Youden Index: Reported for cutoff where the sum of sensitivity and specificity was maximal. It is possible that a higher sum of sensitivity and specificity exists at a cutoff point that was not reported in the respective studies. PPV: positive predictive value, NPV: negative predictive value, +LR: positive likelihood ratio, -LR: negative likelihood ratio

*To have a prediction interval comparable with the one in our tool, we focused here on the API for prediction at 8 years.